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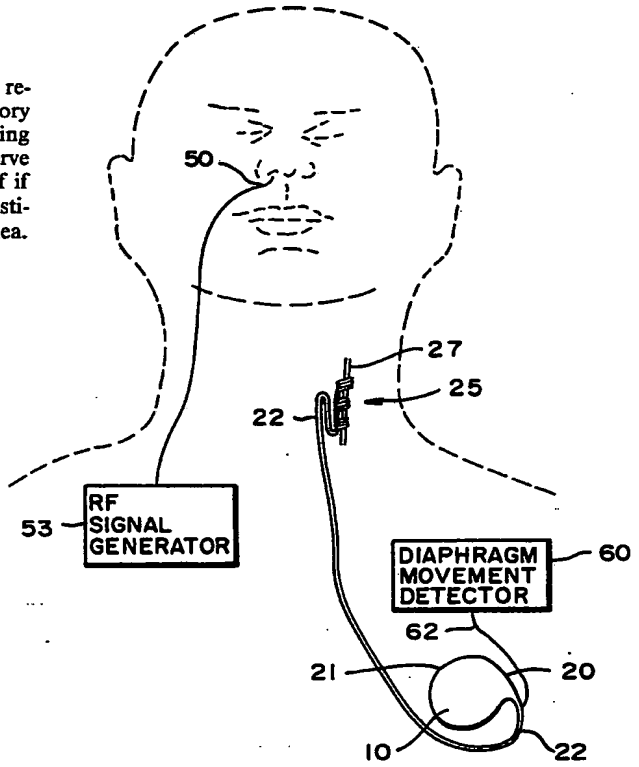
(54) Title: TREATMENT OF RESPIRATORY DISORDERS BY NERVE STIMULATION

(57) Abstract

Method and apparatus for treating and controlling respiratory disorders by detecting the presence of the respiratory disorder under treatment, and, in response, selectively applying a predetermined electrical signal to the patient's vagus nerve for modulation of its electrical activity by inhibition thereof if the respiratory disorder is asthma or cystic fibrosis, or by stimulation of the vagus nerve if the respiratory disorder is apnea.



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TREATMENT OF RESPIRATORY DISORDERS BY NERVE STIMULATION

Background of the Invention

The present invention relates generally to methods and apparatus for treating or controlling medical, psychiatric or neurological disorders by application of modulating electrical signals to a selected nerve or nerves of the patient, and more particularly to techniques for treating patients with respiratory disorders by application of such signals to a cranial nerve, using an implantable neurostimulating device. Specifically, the invention is directed toward treating various respiratory disorders, such as asthma, apnea, and cystic fibrosis by selective modulation of vagus nerve electrical activity.

As a disease entity, asthma is usually idiopathic -- with attacks commonly precipitated by allergic reactions. The attacks are characterized by continuous or paroxysmal labored breathing accompanied by wheezing and a sense of constriction in the chest, and often by coughing or gasping. Apnea is a transient cessation of respiration. Sleep apneas are characterized by brief episodes of respiratory arrest, which may occur many times during sleep and may be associated with obstruction of the upper airways, cessation of diaphragmatic movements and snoring. Cystic fibrosis (CF) is a hereditary disease characterized in part by abnormal secretion in the lungs, leading to difficulty in breathing.

Certain of the respiratory disorders are commonly treated using various drugs and medications. For example, asthma is treated with theopholine, bronchosol, and/or steroids. In the case of apnea, stimulants such as amphetamines are usually adminstered. In contrast, there is presently no significant pharmaceutical treatment of CF; although infections such as pneumonia which are common with CF are treated with antibiotics, and such treatment may be used prophylactically. However, these forms of treatment have not been very effective in all cases, and may cause undesirable side-effects.

It is a principal object of the present invention to apply techniques of selective modulation of the electrical activity of a cranial nerve, and particularly the vagus nerve, to treat and control various respiratory disorders, including asthma, apnea, and cystic fibrosis.

The nerves in the human body are generally composed of thousands of fibers of different sizes designated groups A, B and C, which carry signals to and from the brain and other parts of the body. The vagus nerve, for example, may have approximately 100,000 fibers (axons) of the three different types, each of which carries such signals. Each axon of that nerve only conducts in one direction, in normal circumstances. The A and B fibers are myelinated (i.e., each has a myelin sheath composed largely of fat), whereas the C fibers are unmyelinated. Typically, myelinated fibers are larger, conduct electrical signals faster, and are electrically stimulated at much lower thresholds than unmyelinated fibers. Such fibers exhibit a particular strength-duration curve in response to a specific width and amplitude of stimulation pulse.

The A and B fibers are stimulated with relatively narrow pulse widths, from 50 to 200 microseconds (μs), for example. A fibers exhibit slightly faster electrical conductivities than the B fibers, and slightly lower electrical stimulation thresholds. The C fibers are relatively much smaller, conduct electrical signals very slowly, and have high stimulation thresholds typically requiring wider pulse widths (e.g., 300-1000 μs) and higher amplitudes for activation. Although the A and B fibers may be selectively stimulated without also stimulating the C fibers, the magnitude and width of the pulse required for stimulating the C fibers would also activate A and B fibers.

Electrical stimulation of the nerve fiber typically activates neural signals in both directions (bidirectionally), but selective unidirectional stimulation is achievable through the use of special nerve electrodes and stimulating waveforms.

In a paper on the effects of vagal stimulation on experimentally induced seizures in rats (Epilepsia (1990) 31 (Supp 2): S7-S19), Woodbury has noted that the vagus nerve is composed of somatic and visceral afferents (i.e., inward conducting nerve fibers which convey impulses toward a nerve center such as the brain or spinal cord) and efferents (i.e., outward conducting nerve fibers which convey impulses to an effector to stimulate it and produce activity). The vast majority of vagal nerve fibers are C fibers, and a majority are visceral afferents having cell bodies lying in masses or ganglia in the neck. The central projections terminate largely in the nucleus of the solitary tract which sends fibers to various regions of the brain (e.g, the hypothalamus, thalamus, and amygdala); others continue to the medial reticular formation of the medulla, the cerebellum, the nucleus cuneatus and other regions.

Woodbury further notes that stimulation of vagal nerve afferent fibers in animals evokes detectable changes of the EEG in all of these regions, and that the nature and extent of these EEG changes depends on the stimulation parameters. Chase, in Exp Neurol (1966) 16:36-49, had also observed that vagal activation can affect the EEG activity of certain parts of the brain. Woodbury also observes that vagal stimulation can produce widespread inhibitory effects on seizures and certain involuntary movements.

Extra-physiologic electrical stimulation of the vagus nerve has previously been proposed for treatment of epilepsy and various forms of involuntary movement disorders. Specifically, in U.S. Patent 4,702,254 to J. Zabara (referred to herein as "the '254 patent"), a method and implantable device are disclosed for alleviating or preventing epileptic seizures, characterized by abnormal neural discharge patterns of the brain. The '254 patent describes an implantable neurocybernetic prosthesis (NCP) which utilizes neurocybernetic spectral discrimination by tuning the external current of the NCP generator to the electrochemical properties of a specific group of inhibitory nerves that affect the

reticular system of the brain. These nerves are embedded within a bundle of other nerves, and are selectively activated directly or indirectly by the tuning of the NCP to augment states of brain neural discharge to control convulsions or seizures. According to the patent, the spectral discrimination analysis dictates that certain electrical parameters of the NCP pulse generator be selected based on the electrochemical properties of the nerves desired to be activated. The patent further indicates that the optimum sites for application of the NCP generator output to produce the desired effects are the cranial nerves in general, and the vagus nerve in particular.

The NCP disclosed in the '254 patent may be activated manually or automatically to provide treatment for the duration of the seizure. Manual activation is performed when the patient experiences the aura at onset of the seizure. Alternatively, automatic activation may be triggered upon detection of instantaneous changes in certain state parameters immediately preceding or at onset of a seizure. Additionally, a prophylactic or preventive mode may be employed in which the NCP is activated periodically to reduce the occurrence and/or the intensity of the seizures. The NCP stimulator of the '254 patent is implanted in the patient's chest and is connected to electrodes installed at the selected point of signal application at the nerve site with the more negative electrode situated closer to the brain and the positive electrode further from the brain, along the vagus nerve.

One of the functions of the vagus nerve is to monitor and modulate the diameter of the bronchi. Morrison et al. reported, in Br. J. Pharmacol. (1989) 28:545-549, that patients with asthma have increased vagal activity, leading to increased bronchomotor tone, especially at night; and that increased vagal activity, rather than increased receptor sensitivity, was believed to be the cause for this phenomenon.

Apnea may be induced by any of a variety of known causes, including degenerative diseases of the brain, and brain tumors; or may be idiopathic in origin. The condition is thought to be related to sleep disorders that vary in severity from adult snoring to sudden infant death syndrome. Abnormal control of respiration may lead to apnea. During the waking state, however, the brain stem centers responsible for respiration can be overridden by normal conscious control to initiate breathing. Hence, except for individuals with respiratory failure or serious respiratory control abnormality, only sleep apnea is a problem. A patient suffering from Ondines Curse may completely stop breathing upon falling asleep; but even in sleep apnea condition, the patient is likely to awaken momentarily to breathe, which allows survival, albeit sleep may be fitful.

In J. Appl. Physiol. (1989) 67(6):2249-2256, Holmes et al. found that stimulation of vagal C fibers in cats increases the rate and decreases the depth of respiration (shallow tachypnea), and modulates neuronal discharges to two other muscles (the posterior crycoarytenoid and thyroarytenoid) involved in respiration.

CF is characterized by an excessive quantity of abnormally viscous secretions. These secretions occlude the bronchi, leading to respiratory distress and pneumonia. Since vagal activity is involved in control of bronchial tone, modulation of vagal activity may be useful in increasing bronchial diameter, making it easier to clear secretions.

Summary of the Invention

The invention resides in methods and apparatus for treating respiratory disorders such as asthma, apnea and cystic fibrosis by vagal modulation. The apparatus comprises a neurostimulator for generating electrical pulses in a programmable pattern to produce the desired modulation of vagal electrical activity. According to one aspect of the invention, asthma is treated by inhibiting vagal activity to increase bronchial diameter. Apnea can be treated by

stimulating the vagus nerve, to increase the respiratory rate. In the case of apnea, it is desirable that the neurostimulator which modulates the electrical activity of the vagus nerve be activated by a sensor adapted to detect cessation of breathing. In contrast, patient activation of the neurostimulator is preferable for asthma sufferers, because the patient can readily detect an attack and act accordingly.

As noted above, CF involves abnormal secretions in the lungs. The therapeutic modality employed for this disorder, according to the invention, is to inhibit the vagus nerve to increase bronchial diameter. For this condition, the neurostimulator would operate on a continuous cycle in such a manner as to maintain maximum bronchial diameter or to alternately lead to normal and increased diameter. The latter mode would allow for clearing of accumulated secretions. Activation by the patient may also be desirable to treat acute episodes of respiratory distress.

It is postulated that inhibition of vagal activity can alleviate asthma, irrespective of whether the increased bronchomotor tone results from increased vagal activity or increased receptor sensitivity. Although vagal stimulation is usually associated with activation, parameters can likely be found for effective blocking of efferent activity.

Because the vagus nerve provides feedback to the brain which results in modulation of respiration, it is further postulated that stimulation of the vagus nerve can beneficially treat or control apnea. In copending U.S. patent application Serial No. 07/695,558, the applicants have disclosed techniques for treating and controlling sleep apneas by vagal stimulation. The aspect of the present invention involving apneas is closely related to the latter, but is intended for control of apnea occurring when the patient is fully awake but incapable of exercising conscious control because of respiratory abnormality or failure.

The apparatus of the invention includes a neurostimulator (preferably but not necessarily implantable) to

selectively apply the desired therapy to treat the respiratory disorder of interest by modulating the electrical activity of the patient's vagus nerve in a predetermined manner. The neurostimulator is programmed by the attending physician to provide the desired therapeutic modality for that purpose.

Selection among various strategies for vagal modulation to treat the respiratory disorder of interest depends on a number of factors. These include (i) a consideration of which of the nerve fibers are to be subjected to stimulation; (ii) whether synchronization or desynchronization of the EEG may be desirable, and in either case, the modality for achieving it; (iii) whether some type of physiologic signal is generated which can be detected and employed to trigger the modulation; and/or (iv) whether a "carryover" or refractory period occurs after modulation in which the benefit of the modulation is maintained. Although these are not all of the factors to be considered for selecting a stimulation strategy for treatment of the disorder, nor necessarily listed in order of importance, they are indicative of considerations which may apply in a specific case.

In the treatment according to the invention, different signal parameters and threshold curves are used to activate the various fibers of the patient's vagus nerve for selective modulation of the electrical activity thereof. By appropriately setting pulse width and amplitude of the electrical signal to be delivered by the neurostimulator to the patient's vagus nerve, the nerve fibers can be selectively stimulated, such as A and not B and C; or A and B, but not C; or A, B and C. Various related factors, however, must be considered in the selection process. For example, because the C fibers conduct signals very slowly, they are not highly responsive to techniques of fast stimulation. Therefore, if it were desired to increase desynchronous activity of the EEG by stimulation of the C fibers at 50 Hz, for example, in a particular patient, it would be prudent to use a short pulse train for the stimulus. This is because the fibers would become refractory to the stimulation within a relatively

short time interval and thus incapable of tracking the pattern of a longer train. After a suitable recovery period, another short pulse train may be applied to achieve further treatment. The precise pattern to be used, e.g., the length of the time intervals on and off, will depend upon and be adjusted to the individual patient and the particular respiratory disorder being treated.

Proper designation of amplitude and frequency range of the applied signals allows tuning of the fibers for EEG synchronization or desynchronization, for control of the disorder. Desynchronization of the EEG has been found to be achieved by stimulation of the vagus nerve at frequencies in the range from 20 to 75 Hz at levels above 0.1 volt, but requires signals greater than 3 volts at frequencies above 75 Hz. If the frequency is above 75 Hz and the signal is below 3 volts, EEG synchronization is achieved. The actual voltage required depends on the type and geometry of the electrode and the impedance of the electrode-tissue interface.

According to the invention, the basic stimulation strategy to control asthma or to treat CF is to decrease the electrical activity of the vagus nerve and thereby decrease bronchomotor tone. This involves inhibiting vagal activity and is triggered by manual activation by the patient upon recognizing onset or continuation of the disorder (such as severe difficulty in breathing, along with wheezing, gasping or coughing in the case of asthma). Stimulation (inhibition) may be delivered continuously or intermittently on a predetermined (preprogrammed) schedule so as to keep the bronchi dilated or to intermittently dilate them. For apnea, vagal activity is stimulated to produce an immediate increase in the respiratory rate upon detection of cessation of respiratory muscle (chest) movement or of air flow through the nostril(s).

A stimulation strategy which does not require specific detection involves the use of circadian or other rhythmic programming to automatically activate vagal stimulation in a manner to eliminate respiratory problems, particu-

larly during the normal nighttime cycle. However, a detection strategy may be implemented in each case appropriate to the disorder of interest selected to initiate the proper stimulation strategy.

Broadly, then, the present invention is directed to apparatus and methods which employ a neurostimulator device, preferably implantable, for therapy or treatment of respiratory disorders through nerve stimulation. The modulating signals applied to the vagus nerve may stimulate or inhibit neural signals to produce excitatory or inhibitory neurotransmitter release, but for purposes of this disclosure both situations are included within the term "stimulating". It should be emphasized that although the preferred nerve site for application of the modulating signals is the vagus nerve, effective treatment may be achieved through application of the stimulus to one or more other nerves, particularly among the cranial nerves, and such treatment is deemed to be within the ambit of the present invention.

Accordingly, it is another object of the present invention to apply the techniques of selective modulation of vagus nerve electrical activity, using a neurostimulator device which may be implantable, or disposed external to the body with only a small portion of the circuitry implanted or with only the nerve electrode(s) and associated lead(s) implanted percutaneously in the body, to the treatment or control of respiratory disorders.

A more specific object of the invention is to provide methods and apparatus responsive to detected symptoms characteristic of or associated with certain respiratory disorders for applying preprogrammed electrical stimuli to a cranial nerve and particularly the vagus nerve of the patient to modulate the electrical activity of selected nerve fibers as part of a therapy designed to treat or control the disorder.

Another object of the invention is to provide methods of treating and controlling a respiratory disorder by sensing a symptom of the disorder and automatically or

manually responding thereto by modulating electrical activity of the patient's vagus nerve.

Brief Description of the Drawings

The above and still further objects, aspects, features and attendant advantages of the present invention will be better understood from a consideration of the ensuing detailed description of a presently preferred embodiment and method thereof, taken in conjunction with the accompanying drawings, in which:

FIG. 1 is a simplified block diagram of an implantable neurostimulator (stimulus generator) for use (with appropriate parameter settings and ranges) in treating respiratory disorders according to the present invention;

FIG. 2 is a simplified fragmentary illustration of a preferred embodiment and location of the generator and lead/electrode system of the neurostimulator implanted in the patient's body, and also illustrating the type and placement of suitable sensing devices associated with the neurostimulator for detecting respiratory disorder attacks;

FIG. 3 is a detailed fragmentary illustration of the nerve electrode as implanted on the vagal nerve in the neck of the patient for modulating vagal activity; and

FIG. 4 is an illustrative idealized electrical output signal waveform of the stimulus generator useful for clarifying relevant parameters of the signal developed by the stimulus generator for application to the nerve.

Description of the Presently Preferred Embodiments and Methods

Referring now to the drawings, a block diagram of the basic components of the stimulus generator of a neurostimulator and their interrelationship is illustrated in FIG. 1, and further details of location of an implantable version of the device and the associated lead/electrode system are shown in FIGS. 2 and 3. A generally suitable form of neurostimu-

lator for use in the apparatus of the present invention is disclosed in copending U.S. patent application Ser. No. 07/434,985, filed November 10, 1989 in the names of Anthony J. Varrichio, et al. (referred to herein as "the '985 application"), assigned to the same assignee as the instant application. The specification of the '895 application is incorporated herein in its entirety by reference, but certain portions of it are summarized in this application for the sake of convenience to the reader.

The neurostimulator utilizes a conventional microprocessor and other standard electrical and electronic components, and in the case of an implanted device, communicates with a programmer and/or monitor located external to the patient's body by asynchronous serial communication for controlling or indicating states of the device. Passwords, handshakes and parity checks are employed for data integrity. The neurostimulator also includes means for conserving energy, which is important in any battery operated device and especially so where the device is implanted for medical treatment of a disorder, and means for providing various safety functions such as preventing accidental reset of the device.

The stimulus generator 10 (FIG. 1) is preferably adapted to be implantable in the patient's body, in a pocket formed by the surgeon just below the skin in the chest as shown in FIG. 2, although a primarily external neurostimulator may alternatively be employed. The neurostimulator also includes implantable stimulating electrodes (described below) together with a lead system 22 for applying the output signal of the stimulus generator to the patient's vagus nerve. Components external to the patient's body include a programming wand for telemetry of parameter changes to the stimulus generator and monitoring signals from the generator, and a computer and associated software for adjustment of parameters and control of communication between the generator, the programming wand and the computer. These external components of the system are not shown in the drawings.

In conjunction with its microprocessor-based logic and control circuitry, the stimulus generator 10 or other implanted or external circuitry may include detection circuitry for sensing onset or ongoing presence of the respiratory disorder of interest to trigger automatic delivery of the stimulating signal, as will be discussed presently. In general, however, manual activation of the neurostimulator by the patient is the preferred detection strategy, provided that the patient is capable of recognizing and promptly reacting to the disorder. The stimulus generator is designed, implemented and programmed to deliver a selectively patterned stimulating signal to modulate the electrical activity of the vagus nerve in a manner designed to treat and control the disorder.

As shown in FIG. 1, stimulus generator 10 includes a battery (or set of batteries) 12, which may be of any reliable long-lasting type conventionally employed for powering implantable medical electronic devices (such as batteries employed in implantable cardiac pacemakers or defibrillators). In the preferred embodiment of the stimulus generator, the battery is a single lithium thionyl chloride cell. The terminals of the cell 12 are connected to the input side of a voltage regulator 13. The regulator smoothes the battery output to produce a clean, steady output voltage, and provides enhancement thereof such as voltage multiplication or division if necessary for a specific application.

Regulator 13 supplies power to logic and control section 15, which includes a microprocessor and controls the programmable functions of the device. Among these programmable functions are output current or voltage, output signal frequency, output signal pulse width, output signal on-time, output signal off-time, daily treatment time for continuous or periodic modulation of vagal activity, and output signal-start delay time. Such programmability allows the output signal to be selectively crafted for application to the stimulating electrode set (FIGS. 2 and 3) to obtain the desired modulation of vagal activity for treatment and

control of the specific respiratory disorder. Timing signals for the logic and control functions of the generator are provided by a crystal oscillator 16. A magnetically-actuated reed switch 14 is incorporated in the electronics package to provide the generator with the capability for patient activation thereof (by use of an external magnet, not shown, placed immediately adjacent to the package or its implant site).

Built-in antenna 17 enables communication between the implanted stimulus generator and the external electronics (including both programming and monitoring devices) to permit the device to receive programming signals for parameter changes, and to transmit telemetry information, from and to the programming wand. Once the system is programmed, it operates continuously at the programmed settings until they are reprogrammed (by the attending physician) by means of the external computer and the programming wand.

Logic and control section 15 of the stimulus generator 10 controls an output circuit or section 19 which generates the programmed signal levels appropriate to the disorder being treated. The output section and its programmed output signal are coupled (directly, capacitively, or inductively) to an electrical connector 20 on the housing 21 of the generator and to lead assembly 22 connected to the stimulating electrodes (FIGS. 2 and 3). A sense signal analysis circuit 23 is provided within the generator housing 21, with connections to the microprocessor in logic and control section 15 and to sensing electrodes, if used. The parameters of the stimulating signal of the implanted device may be calibrated by telemetry (via the programming wand) according to the needs of the particular patient and the results then programmed into the microprocessor for delivery of the appropriate treatment upon activation of the stimulus generator.

Housing 21 in which stimulus generator 10 is encased is hermetically sealed and composed of a suitable conventional material such as titanium which is biologically

compatible with the fluids and tissue of the patient's body. Further details of structure and operation of the neurostimulator, beyond those by which the device is adapted to treat the disorder described herein, are available in the '985 application, to which the reader is referred.

FIG. 2 illustrates the preferred location of implanted generator 10, in case 21 with connector 20, in the patient's chest in a cavity formed by the implanting surgeon just below the skin, much as a pacemaker pulse generator would be implanted. A stimulating nerve electrode set 25 (FIG. 3) is conductively connected to the distal end of insulated electrically conductive lead assembly 22 which is attached at its proximal end to connector 20. Electrode set 25 is a bipolar stimulating electrode, preferably of the type described in U.S. Patent 4,573,481 issued March 4, 1986 to Bullara. The electrode assembly is surgically implanted on the vagus nerve 27 in the patient's neck. The two electrodes 25-1 and 25-2 are wrapped about the vagus nerve, and the assembly is secured to the nerve by a spiral anchoring tether 28 preferably as disclosed in U.S. Patent 4,979,511 issued December 25, 1990 to Reese S. Terry, Jr. and assigned to the same assignee as the instant application. Lead(s) 22 is secured, while retaining the ability to flex with movement of the chest and neck, by a suture connection 30 to nearby tissue.

The open helical design of electrode assembly 25 (described in detail in the above-cited Bullara patent), which is self-sizing and flexible, minimizes mechanical trauma to the nerve and allows body fluid interchange with the nerve. The electrode assembly conforms to the shape of the nerve, providing a low stimulation threshold by allowing a larger stimulation contact area. Structurally, the electrode assembly comprises two ribbons of platinum constituting the electrodes which are individually bonded to the inside surface of each of the first two spiral loops 25-1 and 25-2 of a three-loop helical assembly, and the two lead wires are respectively welded to the conductive ribbon electrodes.

The remainder of each loop is composed of silicone rubber, and the third loop acts as the tether 28 for the electrode assembly. The inner diameter of the helical bipolar electrode assembly may typically be approximately two millimeters (mm), and an individual spiral is about seven mm long (measured along the axis of the nerve).

For patients generally suffering respiratory disorders, but especially for apnea patients the cessation of respiration may be detected by an externally-positioned breathing sensor placed in the patient's nostril as shown at 50 in FIG. 2. A suitable breathing sensor merely detects the presence or absence of nasal air flow and is worn in or near one nostril. Processing of the nasal air flow signal is performed by a suitable external circuit 53 (or internal signal analysis circuit 23) which is adapted to generate an activation command to the microprocessor of logic and control circuit 15. A suitable processing/analysis circuit is an RF signal generator which is adapted to be triggered by a sustained absence of nasal air flow for a predetermined interval of time.

Alternatively, a totally implanted sensing system may be employed, if desired, for example using a device which senses movement of the patient's diaphragm associated with normal breathing. Preferably, the diaphragm movement is sensed by an impedance detector, or alternatively, by plural electrodes for detecting physical movement of the muscle, implanted in the chest of the patient as shown generally at 60 in FIG. 2. The detector generates a signal indicative of absence of diaphram movement for a time interval set according to the above-mentioned criteria, which is conveyed by implanted lead 62 to trigger application of vagal stimulation by generator 10 under the command of the microprocessor when it determines a lack of movement. Alternatively, the detector may process the signal and send a trigger signal with absence of movement.

The stimulus generator may be programmed with an IBM-compatible personal computer (not shown) using program-

ming software of the type copyrighted by the assignee of the instant application with the Register of Copyrights, Library of Congress, or other suitable software based on the description herein, and a programming wand (not shown). The wand and software permit noninvasive communication with the generator after the latter is implanted. The wand is preferably powered by internal batteries, and provided with a "power on" light to indicate sufficient power for communication. Another indicator light is preferably provided to show that data transmission is occurring between the wand and the generator.

The operation of stimulus generator 10 to control and treat respiratory disorders utilizes the signal parameters shown in FIG. 4, which is an idealized representation of the output signal waveform delivered by output section 19 of the neurostimulator to electrode assembly 25. This illustration is presented principally to clarify terminology, including the parameters of output signal on-time, output signal off-time, output signal frequency, output signal pulse width, and output signal current or voltage.

In the treatment of asthma or CF according to the invention, the stimulation strategy is to decrease the patient's vagal activity and thereby decrease the bronchomotor tone, especially at night. The detection strategy for automatic activation of the neurostimulator to that end is to sense either air flow or the amount of vagal activity in a manner which will be discussed in greater detail presently. Preferably, however, the patient suffering from asthma or cystic fibrosis is provided with the capability to manually activate the neurostimulator when the onset of an attack is sensed. This is readily accomplished by placing an external magnet directly over the site of the implanted stimulus generator to actuate the reed switch 14 (FIG. 1).

A suitable range of stimulation parameters and the typical value of each parameter of the stimulating output signal for treatment of asthma or CF are set forth in Table I below:

TABLE I

	Range	Typical
Pulse Width	0.05 - 1.5 ms	0.5 ms
Output Current	0.1 - 5.0 mA	1.5 mA
Frequency	5 - 150 Hz	100 Hz
ON Time	5 - 5000 sec	500 sec
OFF Time	5 - 5000 sec	10 sec
Frequency sweep	10 - 50 Hz	Optional
Random frequency	10 - 50 Hz	Optional

A technique for initiating stimulation without a detection system, either machine sensor or patient sensing, is to program the neurostimulator for activation according to the circadian rhythm of the particular patient and the disorder being treated. For example, the stimulus generator may be programmed to generate its pulses with the selected parameters at one or more set times during the night. Alternatively, automatic detection and stimulation may be employed during the patient's normal sleeping hours, and biased off during the day to require manual activation in that portion of the 24-hour cycle.

In contrast to treating asthma by inhibiting vagal activity to increase bronchial diameter such as when the patient senses an attack, apnea is treated by stimulating the vagus nerve to increase the respiratory rate upon automatic detection of sustained cessation of breathing. Air flow or chest movement sensors of the types described above with reference to FIG. 2 are preferred. The stimulation strategy involves programming the neurostimulator to desynchronize the apnea patient's EEG activity upon such detection, and thereby increase respiration. For desynchronization, the parameters of the stimulus signal may be programmed, for example, at a frequency of 20 Hz, an output current of 1.5 mA, and a pulse width of 0.5 ms for the pulse waveform. A suitable range of stimulation parameters for desynchronization of the patient's EEG activity, and the typical value of each parameter of the stimulating output signal for treatment of apnea are set forth in Table II:

TABLE II

	Range	Typical
Pulse Width	0.05 - 1.5 ms	0.5 ms
Output Current	0.1 - 5.0 mA	1.5 mA
Frequency	5 - 150 Hz	20 Hz
ON Time	5 - 5000 sec	300 sec
OFF Time	5 - 5000 sec	20 sec
Frequency sweep	10 - 100 Hz	Optional
Random frequency	10 - 100 Hz	Optional

As noted earlier herein, a technique for initiating stimulation without a specific detection system is to program the neurostimulator according to the circadian rhythm of the particular apnea patient, or intermittently, to desynchronize the patient's EEG activity as appropriate.

A secondary mode of stimulation for treating apnea patients, which may be employed either as an alternative or as an adjunct to the previously described operation, is to apply a painful stimulus such as a mild electric shock to the patient either at the end of the initial time interval with no breathing or after a subsequent shorter time interval indicative of no response by the patient to the normal pulse stimuli from the neurostimulator. The purpose here is to bring the patient back to consciousness and thereby restore breathing through conscious control.

Various features may be incorporated into the neurostimulator for purposes of the safety and comfort of the patient. For example, comfort is enhanced by programming the output stimulus to ramp up during the first two seconds of

stimulation, rather than to be delivered abruptly. Also, the implanted generator may be provided with a clamping circuit to limit the maximum voltage delivered to the vagus nerve (for example, to 14 volts). The maximum limit is set to prevent injury or trauma to the patient's vagus nerve.

The programmable functions and capabilities of the neurostimulator are designed and implemented to permit noninvasive communication with the stimulus generator after it is implanted, which is useful for both activation and monitoring functions. Beyond the essential functions of the device, the programming software may readily be structured to provide straightforward menu-driven operation, HELP functions, prompts, and messages to facilitate simple and rapid programming while keeping the user fully informed of everything occurring at each step of a sequence. Programming capabilities should include capability to modify the adjustable parameters of the stimulus generator and its output signal, to test device diagnostics, and to store and retrieve telemetered data. It is desirable that when the implanted unit is interrogated, the present state of the adjustable parameters is displayed on the monitor of external PC so that the programmer may then conveniently change any or all of those parameters at the same time; and, if a particular parameter is selected for change, all permissible values for that parameter are displayed so that the programmer (typically, limited to the attending physician) may select an appropriate desired value for entry into the neurostimulator.

Diagnostics testing should be implemented to verify proper operation of the device, and to indicate the existence of problems such as with communication, the battery, or the lead/electrode impedance. A low battery reading, for example, would be indicative of imminent end of life of the battery and need for implantation of a new device. The nerve electrodes are capable of indefinite use absent indication of a problem with them observed on the diagnostics testing.

Although a preferred embodiment and method of controlling respiratory disorders have been described herein, it will be apparent to those skilled in the field from a consideration of the foregoing description that variations and modifications may be made without departing from the spirit and scope of the invention. For example, a totally implantable neurostimulator device need not be utilized. Instead, the electronic energization package may be primarily external to the body, and stimulation achieved with an RF power device implemented to provide the necessary energy level. The implanted components may be limited to the lead/electrode assembly, a coil and a DC rectifier, and pulses programmed with the desired parameters transmitted through the skin with an RF carrier. The signal is rectified to regenerate a pulsed signal for application as the stimulus to the vagus nerve to modulate vagal activity. This virtually eliminates battery changes, but has the disadvantages that the external transmitter must be carried by the patient, greater power is required for activation, and the output current to the nerve is less stable.

An external stimulus generator may be employed with leads extending percutaneously to the implanted nerve electrode set. The major problem here is the potential for infection, but it is useful to allow short term testing of the patient to determine whether the disorder suffered by the patient under observation is amenable to successful treatment. If it is, a more permanent implant may be provided.

Accordingly, it is intended that the invention shall be limited only to the extent required by the appended claims and the rules and principles of applicable law.

What is claimed is:

1. A method of treating patients with respiratory disorders, which includes

detecting an event indicative of the respiratory disorder to be treated, and

upon detection of said event, selectively applying a predetermined electrical signal to the patient's vagus nerve for stimulation thereof to alleviate the respiratory disorder under treatment.

2. The method of claim 1, wherein

the predetermined electrical signal is programmable to modulate the electrical activity of the vagus nerve and thereby control another physiological parameter of the patient.

3. The method of claim 2, wherein

the predetermined electrical signal is a pulse waveform with programmable signal parameters.

4. The method of claim 1, wherein

the event is detectable by the patient, and the electrical signal is manually activatable.

5. The method of claim 3, wherein

the respiratory disorder is asthma, and

the pulse waveform is programmed to inhibit vagal activity to increase bronchial diameter.

6. The method of claim 3, wherein

the respiratory disorder is cystic fibrosis, and

the pulse waveform is programmed to inhibit vagal activity to increase bronchial diameter.

7. The method of claim 3, wherein

the respiratory disorder is apnea, and

the pulse waveform is programmed to stimulate vagal activity to increase the respiratory rate upon automatic detection of sustained cessation of breathing.

8. The method of claim 7, wherein

the predetermined signal has electrical parameters programmed to cause desynchronization of the patient's EEG.

9. The method of claim 7, further including

applying a painful stimulus to awaken the patient upon failure of initiate breathing by the patient in response to the programmed pulse waveform.

10. The method of claim 3, wherein

the programmable signal parameters of the pulse waveform include at least some of pulse width, output current or voltage, frequency, on time and off time.

11. In a method of treating patients with respiratory disorders, the step of applying an electrical signal with parameters programmed to alleviate the respiratory disorder under treatment to the vagus nerve of the patient to modulate the electrical activity thereof at predetermined times and for predetermined time intervals during the patient's circadian cycle.

12. A device for treating respiratory disorders in human patients, the combination comprising:

stimulus means for generating a programmable electrical waveform,

implantable electrode means electrically connectable to said stimulus means for delivering said waveform to the vagus nerve of the patient, and

programming means for applying said waveform to said electrode means with selected parameter values of the waveform programmed to stimulate the vagus nerve to modulate the electrical activity thereof according to the nature of the respiratory disorder under treatment.

13. The invention of claim 12, wherein

said programming means includes means for selecting the parameter values of the waveform to inhibit or to stimulate the electrical activity of the patient's vagus nerve according to whether the respiratory disorder under treatment is difficulty in breathing or complete cessation of breathing, respectively.

14. The invention of claim 12, further including

sensing means to detect an event indicative of onset of the respiratory disorder under treatment, for initiating the application of said waveform to said electrode means.

15. The invention of claim 12, wherein

said programming means applies said waveform to said electrode means at predetermined times and for predetermined time intervals during the patient's circadian cycle.

16. The invention of claim 14, wherein

said sensing means includes means for detecting a cessation of respiration of the patient.

17. The invention of claim 16, wherein

said means for detecting cessation of respiration includes means responsive to the absence of movement of the patient's diaphragm.

18. The invention of claim 16, wherein

said means for detecting cessation of respiration includes means responsive to the absence of nasal air flow by the patient.

19. The invention of claim 16, wherein

the parameter values of the waveform are selected by said programming means to stimulate vagal activity and thereby increase the patient's respiration rate.

20. The invention of claim 19, wherein

the stimulation of vagal activity desynchronizes the patient's EEG.

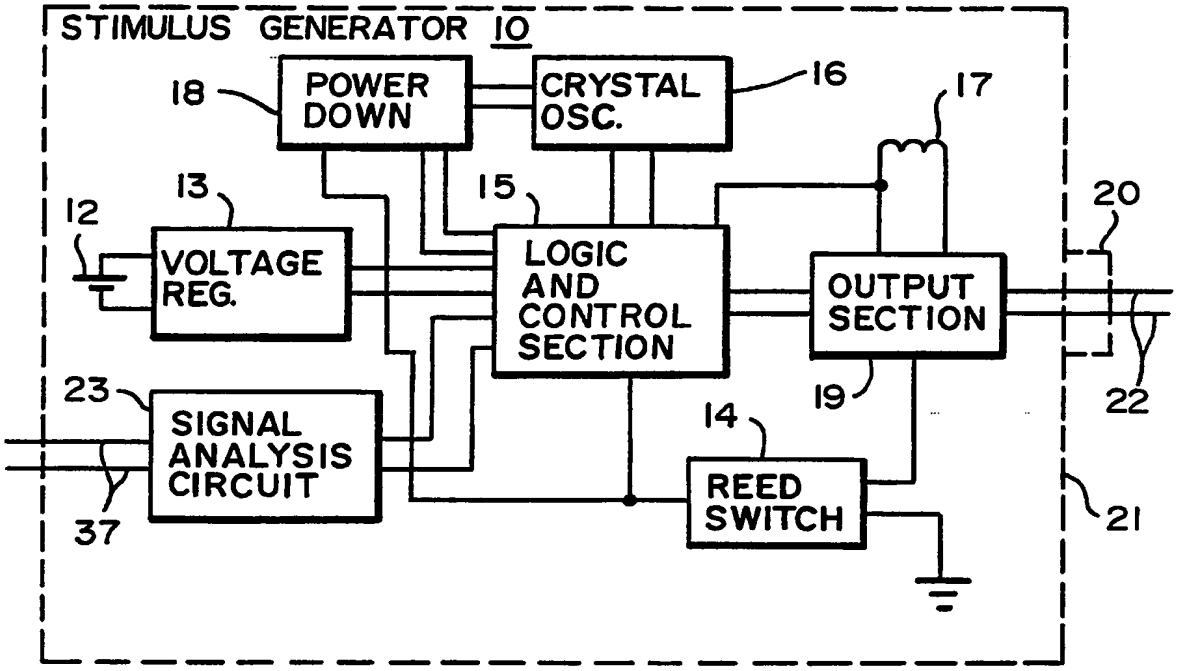
STIMULUS GENERATOR 10
18
POWER DOWN
CRYSTAL OSC.
16
17
13
15
12
VOLTAGE REG.
LOGIC AND CONTROL SECTION
OUTPUT SECTION
20
23
SIGNAL ANALYSIS CIRCUIT
19
22
14
REED SWITCH
21
37

FIG. 1

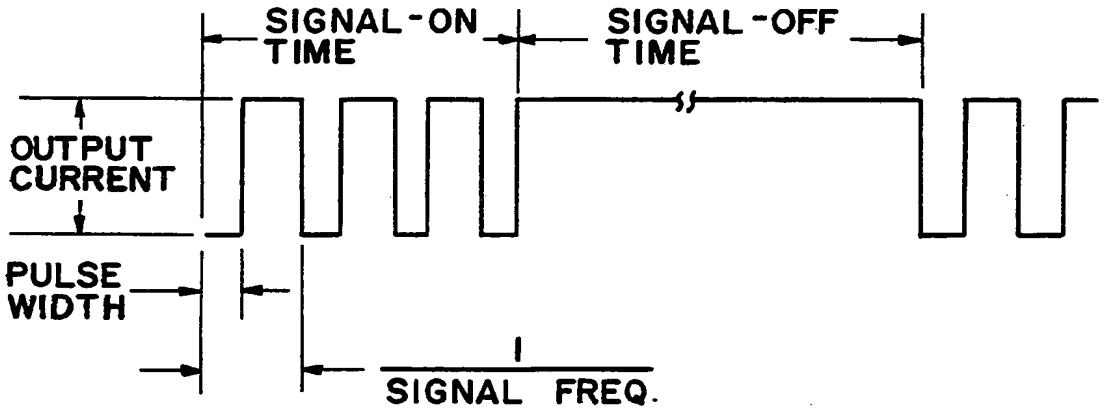
SIGNAL-ON TIME
SIGNAL-OFF TIME
OUTPUT CURRENT
PULSE WIDTH
1
SIGNAL FREQ.

FIG. 4

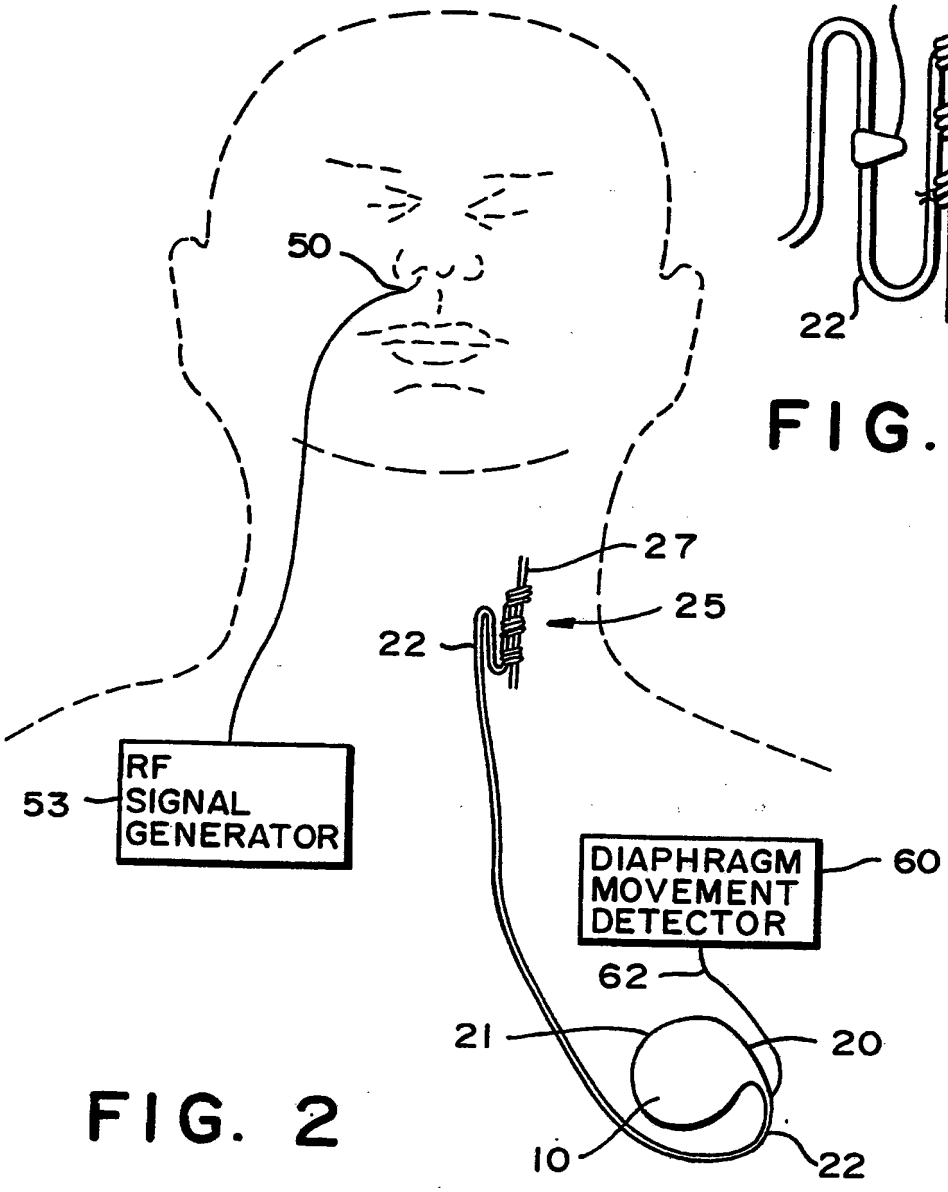
50
27
25
22
RF
SIGNAL
GENERATOR
53
DIAPHRAGM
MOVEMENT
DETECTOR
60
62
21
20
10
22

FIG. 2

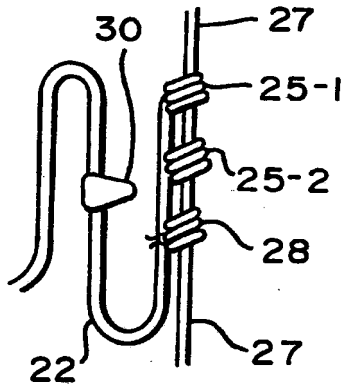
30
27
25-1
25-2
28
22
27

FIG. 3

INTERNATIONAL SEARCH REPORT

PCT/US92/05980

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61N 1/36
US CL :128/421

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/419.OOG,419.OOR,422,423.OOR,716,721,724,725

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

N/A

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A, 2,664,880 (WALES, JR.) 05 JANUARY 1954.	
A,P	US,A, 5,036,848 (HEWSON) 06 AUGUST 1991.	
A	US,A, 4,830,008 (MEER) 16 MAY 1989.	
A	US,A, 4,063,550 (TIEP) 20 DECEMBER 1977.	
A	US,A, 5,025,807 (ZABARA ET AL) 25 JUNE 1991.	

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
13 DECEMBER 1992	04 JAN 1993
Name and mailing address of the ISA/ Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer WILLIAM E. KAMM
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-0858

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/05980

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	EP,A, 0,293,068 (HASEGAWA ET AL) 30 NOVEMBER 1988.	
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A,P	WO,A1,91/17706 (REITEN ET AL) 28 NOVEMBER 1991.	
A	SU,A, 1,194,416 (PORTNOV) 30 NOVEMBER 1985.	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/05980

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"Journal of Thoracic and Cardio Vascular surgery, Volume 5f, November 1, July 1968, Bilgutay, A.M., ET AL, "VAGAL TUNING". pp. 71-82 (See page 73).	12-13 and 15